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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/645,756	MONAHAN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 49-55* is/are pending in the application.

4a) Of the above claim(s) *11-15 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,16-21 and 49-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050815*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The election without traverse filed September 20, 2006, is acknowledged and has been entered.

Applicant has elected the invention of Group I, claims 8-10, drawn to a method for assessing whether a person is afflicted with cervical cancer, said method comprising detecting the presence in a sample of one or a plurality of proteins corresponding to one or a plurality of markers, wherein said markers are selected from the group consisting of M1A, M718, OV3A, M719, M720, M5A, M10A, M29A, M30A, M721, M488A, M35, M722, M723, M666, M489A, AV43A, M51A, M58, M22A, M74A, and M78, as listed in Table 1 of the specification.

Furthermore, Applicant has elected the species of the invention of Group I, wherein said one or a plurality of markers is the marker identified as M666.

Claims 1-7 and 16-21 are linking claims, linking the inventions of Groups I and II.

2. The amendment filed September 20, 2006, is acknowledged and has been entered. Claims 22-48 have been canceled. Claim 2 has been amended. Claims 49-55 have been added.

3. Claims 1-21 and 49-55 are pending in the application. Claims 11-15 and 55 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 20, 2006.

4. Claims 1-10, 19-21, and 49-54 are currently under prosecution.

Information Disclosure Statement

5. The information disclosure filed August 10, 2005, has been considered. An initialed copy is enclosed.

Response to Amendment

6. The amendment filed on September 20, 2006, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution, rather than mailing a Notice of Non-Compliant Amendment, Applicant is advised to correct the following deficiency in replying to this Office action:

The amendment is non-compliant because the listing of claims incorrectly indicates that claims 4 and 11-15 were withdrawn at the time the amendment was filed; and moreover, only claims 11-15 have been withdrawn by this Office action.

Only the corrected section of the non-compliant amendment must be resubmitted (in its entirety), e.g., the entire "Amendments to the claims" section of applicant's amendment must be re-submitted. 37 CFR § 1.121(h).

Election/Restrictions

7. Newly submitted claim 55 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claim 55 is drawn to a product, namely a kit comprising reagents; and in contrast, the elected invention is a process for assessing whether a patient is afflicted with cervical cancer or has a pre-malignant condition.

Inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See M.P.E.P. § 806.05(h).

Although claim 55 recites the intention that the claimed product be used to perform the method of claim 1, the kit and its components may be used to practice other processes that utilize reagents. For example, if the reagent were a detectably labeled secondary antibody having affinity for a primary antibody, it is used in the process of detecting a complex of the primary antibody and the antigen to which the primary antibody binds.

Because elected invention and the subject matter of the newly added claim are distinct for these reasons, and also because the search required for examination of the subject matter of the newly added claims and the search required for examination of the elected group is not co-extensive, and because the subject matter of the elected group and the subject matter of the newly added claims has acquired a separate status in the art as shown by their different classification or are recognized as being divergent, restriction for examination purposes as indicated is deemed proper.

Accordingly, claim 55 has been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

Priority

8. Applicant's claim under 35 USC § 119(e) for benefit of the earlier filing date of the U.S. Provisional Application No. 60/404,770, filed August 20, 2002, is acknowledged.

However, claims 1-10, 19-21, and 49-54 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of claims 1-10, 19-21, and 49-54 is deemed the filing date of the instant application, namely August 20, 2003.

Specification

9. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such an impermissible disclosure, which appears in this application, is found in the specification at page 38, lines 19 and 20.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

10. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in this application is Primer Express™ (see, e.g., page 92, line 27).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-10, 16-21, and 49-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10, 16-21, and 49-54 are indefinite for the following reasons:

(a) Claim 1 recites, "a pre-malignant condition". Is the claimed process a method for assessing whether a patient is afflicted with a pre-malignant condition of the cervix, or just any pre-malignant condition?

(b) Claim 2 recites, "wherein the patient has cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL)". Is the claimed process a method for assessing whether a patient that has CIN or SIL is afflicted with cervical cancer or a pre-malignant condition of the cervix, or a method for assessing whether the patient is afflicted with CIN or SIL? It cannot be determined how claim 2 is intended to further limit the subject matter of the preceding claim.

(c) Claim 3 recites, "wherein the marker corresponds to a secreted protein". At paragraph [0071] of the published application, the specification defines the term "marker" as meaning "a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer"; however, the same disclosure appears to describe the "marker" as inclusive of a "nucleic acid marker" (e.g., mRNA, cDNA) encoded by or corresponding to a marker of the invention, or a "marker protein" is a "protein marker" encoded by or corresponding to a marker of the invention, which comprises the entire or a partial sequence of any of the disclosed sequences set forth in the Sequence Listing. Accordingly, it is not clear how the marker to which claim 3 is directed must *correspond* to a secreted protein. Is the marker a nucleic acid molecule encoding a secreted protein, or is the marker a secreted protein or fragment thereof?

(d) Claim 4 recites, "wherein the marker corresponds to a transcribed polynucleotide or portion thereof, wherein the polynucleotide comprises the marker". Given the above-mentioned disclosure at paragraph [0071] of the published application, it cannot be determined how the marker to which claim 4 is directed necessarily *corresponds* to a transcribed polynucleotide comprising the marker or a portion thereof. Is the marker the transcribed nucleic acid molecule or a portion thereof? Is the transcribed nucleic acid molecule or a portion thereof the marker? Given this apparent lack of clarity and particularity, it is submitted that claim 4 fails to adequately delineate the subject matter that Applicant regards as the invention, so as to permit the skilled artisan to know or determine infringing subject matter and satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(e) Claims 5, 6, 8, 16, 17, 18, and 51 recite the limitation, "the sample". The preceding claim recites "a patient sample" and "a normal control cervical cancer sample". It cannot be determined to which of these samples any of claims 5, 6, 8, 16, 17, 18, and 51 refer.

(f) Claim 5 recites, "wherein the sample comprises an adenocarcinoma cell". Is the adenocarcinoma cell necessarily a cervical adenocarcinoma cell, or might it be any adenocarcinoma cell?

(g) Claim 18 recites, "in samples of the same type". While it is evident that the samples are obtained from normal control human cervical samples, it is not apparent to what or which "type" the claim refers? Are the samples obtained from normal control human cervical samples comprised of the same *type* of tissue or cell as tissue or cell of which the patient sample is comprised?

(h) Claim 51 recites, "wherein the sample comprises an adenocarcinoma cell". Is the adenocarcinoma cell necessarily a cervical adenocarcinoma cell, or might it be any adenocarcinoma cell?

(i) Claim 52 recites, "wherein the sample comprises an squamous cell". Is the squamous cell necessarily a cervical squamous cell, or might it be any squamous cell?

In summary, given the ambiguity with which the claims might be interpreted, and/or their apparent lack of clarity and particularity, it is submitted that they fail to adequately delineate the subject matter that Applicant regards as the invention, so as to permit the skilled artisan to know or determine infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-10, 16-21, and 49-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In this instance, the claims are directed to a method for assessing whether a patient is afflicted with cervical cancer or has a pre-malignant condition, said method comprising detecting the presence in a sample of one or a plurality of proteins corresponding to one or a plurality of markers, wherein the one or a plurality of markers is, or includes M666, as identified in Table 1 of the specification.

The specification, however, does not describe the claimed invention with the particularity necessary to reasonably convey its possession by the Applicant at the time the application was filed, since, for example, it merely describes the expression of the

protein in a cervical tumor (i.e., cervical adenocarcinoma and squamous cell carcinoma), as well as the lack thereof by normal cervical tissue; see, e.g., Tables 4 and 8 of the specification.

As such, the specification does not describe with any degree of the requisite particularity the presence of the protein in any non-cervical biological sample, such as the blood or the saliva; and given the fact that marker M666 is described as encoding KCNAB1, the beta subunit of a potassium voltage-gated channel, it is not expected this particular protein is *not* normally secreted, or would be present in the serum or any other biological fluid specimen, which is not expected to comprise cervical tumor cells. Yet, claim 3 is specifically directed to the method of claim 1, wherein the marker corresponds to a secreted protein.

Moreover, the specification does not describe the presence of the protein in any biological sample, which does not comprise cervical tumor cells. Yet, while claims 5-7 require the sample comprise cells, those cells are not necessarily the cells of a cervical tissue. Furthermore, while claims 51-54 require the samples comprise an adenocarcinoma cell or a squamous cell, those cells are not necessarily cervical cells; and none of the remaining claims are directed to samples comprising cells of any type.

In addition, although claim 2 requires the patient have CIN or SIL, there is no clear and particular description of a significant overexpression of the protein encoded by marker M666 by any specific type of cervical tumor cell or pre-malignant cell, apart from the cervical adenocarcinoma cell and the squamous cell carcinoma cell (Tables 4 and 8). According to Table 4, for example, high-grade squamous intraepithelial lesions (HSIL) do not significantly overexpress this protein (i.e., KCNAB1); and the specification simply does not address the expression of the protein by CIN or low-grade squamous intraepithelial lesions (LSIL).

At paragraph [0011] of the published application, the specification defines "cervical cancer" as inclusive of carcinomas, (e.g., carcinoma in situ, invasive carcinoma, metastatic carcinoma) and pre-malignant conditions, (e.g., dysplasia, including CIN or SIL). Then, at paragraph [0125] of the published application, the specification further describes "cervical cancer" and pre-malignant lesions to include

cervical cancer of various stages (i.e., stage 0, I, II, III, and IV cervical cancers, as well as subclassifications IA1, IA2, IB, IB1, IB2, IIA, IIB, IIIA, IIIB, IVA, and IVB) and pre-malignant conditions (e.g., dysplasia including CIN or SIL), of various histologic subtypes (e.g. squamous cell carcinomas and squamous cell carcinoma variants such as verrucous carcinoma, lymphoepithelioma-like carcinoma, papillary squamous neoplasm and spindle cell squamous cell carcinoma, serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal (Mullerian) mixed tumor, malignant carcinoma, mixed epithelial tumor, and undifferentiated carcinoma, and various grades (i.e., grade I, grade II, and grade III).

The skilled artisan cannot predict whether the protein encoded by marker M666 is differentially expressed by cervical cancer cells and pre-malignant cervical cells, such as CIN or LSIL cells, because the specification teaches, for example, while MCM 6 is overexpressed in high-grade squamous intraepithelial lesions (HSIL), claudin 1 is only overexpressed in squamous cell carcinoma (page 90, lines 14-16), and neither MCM 6 nor claudin 1 are significantly overexpressed by low-grade squamous intraepithelial lesions (LSIL) (see, e.g., Figure 2). Accordingly, it follows one cannot predict whether KCANB1, the protein encoded by marker M666 is overexpressed in any given type of cervical cell (e.g., LSIL, CIN, or any of the serous, mucinous, endometrioid, and clear cell subtypes of cervical cancer), apart from squamous cell carcinoma cells and adenocarcinoma cells.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Furthermore, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69

USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of "cervical cancers and pre-malignant conditions", the presence of which in a patient can be assessed by comparing the levels of the polypeptide encoded by marker M666 in samples acquired from the patient and a normal control.

As to whether the claimed process may be used to assess whether a patient is afflicted with a pre-malignant condition, although the specification describes such conditions as inclusive of dysplasias, such as CIN and SIL, the claims are not so limited, and it is aptly noted that the particular features that characterize "pre-malignant" cells are not disclosed in the specification. So, inasmuch as any *normal* cell might be the progenitor of a cancer cell, it is fairly said that any cell is "pre-malignant". Yet, the specification would not reasonably convey that Applicant was in possession of such an invention for assessing the presence in a patient of any such cell that might later give rise to a cancer, as it has not been shown that such cells differentially express any one of the proteins encoded by the described markers, including that which is encoded by marker M666.

With further regard to claim 9, which is directed to a genus of "reagents" that specifically bind the protein, while the specification adequately describes an antibody or antigen-binding fragment thereof, which binds to the polypeptide encoded by marker M666, it does not adequately describe the genus as a whole, nor does it adequately describe the "antibody derivative" to which claim 10 is directed, as the antibody that binds this protein is not representative of the genus. While the reagent to which the claims are directed necessarily binds the protein, it does not have any particular structure; as such, there is no correlation between any one particularly identifying structural feature, which is shared by members of the genus of "reagents", and their common ability to bind the protein. For this reason, the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of members of the genus of reagents to which the claims are directed.

The Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to bind to a protein, does not

provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding a "reagent" that has the ability to bind to the protein, which can be used to practice the claimed invention to assess whether the patient is afflicted with cervical cancer or a pre-malignant condition; without such a reagent, it is impossible to practice the invention.

In addition, although the skilled artisan could potentially identify such reagents that might be used in practicing the claimed invention by screening for substances (e.g., peptides and small organic molecules) that are capable of binding the protein, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*.

> The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Finally, Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of substances having the common ability to bind a protein, but no particular or shared structure, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

15. Claims 1-10, 16-21, and 49-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for assessing whether a patient is afflicted with adenocarcinoma or squamous cell carcinoma of the cervix, said method comprising determining whether the polypeptide comprising the amino acid sequence of SEQ ID NO: 30 (i.e., KCNAB1), which is encoded by marker M666 comprising the polynucleotide sequence of SEQ ID NO: 29, is overexpressed in a

sample of cervical tissue acquired from the patient, as compared to its level of expression in a sample of cervical tissue acquired from normal control subject not afflicted by cervical cancer, **does not reasonably provide enablement for using** a method for assessing whether a patient is afflicted with cervical cancer or has a pre-malignant condition, said method comprising comparing the level of expression of one or a plurality of markers in a patient sample to the level of expression of the one or more markers in "a normal control cervical cancer sample", wherein a significant difference between these levels provides an indication that the patient is afflicted by cervical cancer or has a pre-malignant condition, and wherein said one or more marker is, or includes M666, and the level of expression of the marker in the sample is assessed by detecting the presence in the sample of a protein corresponding to the marker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth

of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the "written description" rejection above, the claims are drawn to a method for assessing whether a patient is afflicted with cervical cancer or has a pre-malignant condition, said method comprising detecting the presence in a sample of one or a plurality of proteins corresponding to one or a plurality of markers, wherein the one or a plurality of markers is, or includes M666, as identified in Table 1 of the specification.

The specification, however, only teaches the expression of the protein in a cervical tumor (i.e., cervical adenocarcinoma and squamous cell carcinoma), as well as the lack thereof by normal cervical tissue; see, e.g., Tables 4 and 8 of the specification.

As such, the specification does not teach whether or not the presence of the protein in any non-cervical biological sample, such as the blood or the saliva, provides an indication that the patient is afflicted with cervical cancer or a pre-malignant condition; but given the fact that marker M666 is described as encoding KCNAB1, the beta subunit of a potassium voltage-gated channel, it would not be reasonably expected that this particular protein is secreted into the bloodstream or other bodily fluids (e.g., urine). As such, it would not be expected to be present in the serum or any other biological fluid specimen, particularly any such fluid that does not comprise cervical tumor cells. Yet, claim 3 is specifically directed to the method of claim 1, wherein the marker corresponds to a secreted protein.

Moreover, the specification does not teach whether or not the presence of the protein in any biological sample, which does not comprise cervical tumor cells, is indicative of the presence in the patient of cervical cancer or a pre-malignant condition. Notably, while claims 5-7 require the sample comprise cells, those cells are not

necessarily the cells of a cervical tissue. Furthermore, while claims 51-54 require the samples comprise an adenocarcinoma cell or a squamous cell, those cells are not necessarily cervical cells; and none of the remaining claims are directed to samples comprising cells of any type.

In addition, although claim 2 requires the patient have CIN or SIL, the specification does not teach whether or not there is significant overexpression of the protein encoded by marker M666 by any specific type of cervical tumor cell or pre-malignant cell, apart from the cervical adenocarcinoma cell and the squamous cell carcinoma cell (Tables 4 and 8). According to Table 4, for example, high-grade squamous intraepithelial lesions (HSIL) do not significantly overexpress this protein (i.e., KCNAB1); and the specification simply does not address the expression of the protein by CIN or low-grade squamous intraepithelial lesions (LSIL).

At paragraph [0011] of the published application, the specification defines "cervical cancer" as inclusive of carcinomas, (e.g., carcinoma in situ, invasive carcinoma, metastatic carcinoma) and pre-malignant conditions, (e.g., dysplasia, including CIN or SIL). Then, at paragraph [0125] of the published application, the specification further describes "cervical cancer" and pre-malignant lesions to include cervical cancer of various stages (i.e., stage 0, I, II, III, and IV cervical cancers, as well as subclassifications IA1, IA2, IB, IB1, IB2, IIA, IIB, IIIA, IIIB, IVA, and IVB) and pre-malignant conditions (e.g., dysplasia including CIN or SIL), of various histologic subtypes (e.g. squamous cell carcinomas and squamous cell carcinoma variants such as verrucous carcinoma, lymphoepithelioma-like carcinoma, papillary squamous neoplasm and spindle cell squamous cell carcinoma, serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal (Mullerian) mixed tumor, malignant carcinoma, mixed epithelial tumor, and undifferentiated carcinoma, and various grades (i.e., grade I, grade II, and grade III).

As explained, the skilled artisan cannot predict whether the protein encoded by marker M666 is differentially expressed by cervical cancer cells and pre-malignant cervical cells, such as CIN or LSIL cells, because the specification teaches, for example, while MCM 6 is overexpressed in high-grade squamous intraepithelial lesions (HSIL), claudin 1 is only overexpressed in squamous cell carcinoma (page 90, lines 14-16), and neither MCM 6 nor claudin 1 are significantly overexpressed by low-grade squamous intraepithelial lesions (LSIL) (see, e.g., Figure 2). Accordingly, it follows one cannot predict whether KCANB1, the protein encoded by marker M666 is overexpressed in any given type of cervical cell (e.g., LSIL, CIN, or any of the serous, mucinous, endometrioid, and clear cell subtypes of cervical cancer), apart from squamous cell carcinoma cells and adenocarcinoma cells. The specification does not teach whether KCANB1 is differentially expressed by most other histological subtypes of cervical cancer, nor does it teach whether the protein is overexpressed in CIN, LSIL, and other dysplastic, pre-malignant conditions of the cervix or other tissues.

In addition, according to claim 1, the invention is a method for assessing whether a patient is afflicted with cervical cancer or has a pre-malignant condition, said method comprising comparing the level of expression of one or a plurality of markers in a patient sample to the level of expression of the one or more markers in "a normal control cervical cancer sample", wherein a significant difference between these levels provides an indication that the patient is afflicted by cervical cancer or has a pre-malignant condition. If the "normal" level is the level of expression in a specimen of cervical cancer cells, as the claims recite, then, that level is not expected to differ from the level of expression in a sample of cervical cancer cells acquired from the patient. Moreover, it is submitted that the claimed invention could not be practiced, as it would not be possible to assess the presence of cervical cancer or a pre-malignant condition in a patient by comparing the level of the polypeptide encoded by marker M666 in a sample acquired from a patient and a sample of cervical cancer cells, if the patient is so afflicted.

Claim 4 is directed to the method of claim 1, wherein the marker corresponds to a transcribed polynucleotide or portion thereof, and the elected invention is a method

according to claim 1, wherein the level of expression of the marker is assessed by detecting the presence in the sample of a protein corresponding to the marker. Notably, the presence of the protein encoded by the transcribed polynucleotide *alone* would not provide a measure of the level of expression of the marker; rather, at the very least, it would be necessary to measure the level of the protein to assess the level of expression of the marker. Nonetheless, because, for example, transcription and translation are processes, which are not necessarily coordinately regulated within any given cell, it is possible the level of the protein may not accurately reflect the level of expression of the marker at the time the assessment is made. As another example, because the half-life of the transcribed mRNA is relatively short, whereas the lifetime of the protein encoded by that mRNA may be substantially longer, again, the level of the protein may not provide an indication as to the level at which the marker is expressed.

Claims 16, 17, 53, and 54 recite the level of expression of the marker in the sample differs from the normal level of expression of the marker in a patient not afflicted with cervical cancer; yet, the normal level of expression is not necessarily the normal level of expression in the cervix, but might instead be the normal level of expression in some other tissue specimen acquired from a patient not afflicted by cervical cancer. The specification fails to provide sufficient guidance and direction to select other non-cervical tissues for use as appropriate controls in establishing the "normal" level of expression to be used as the basis for the comparison and determination that the patient is afflicted with cervical cancer or a pre-malignant condition, since the skilled artisan cannot predict which, if any, other tissues might provide such appropriate controls.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 1, 2, 4-10, 16-21, and 49-54 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication No. 2003/0087270 A1.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

U.S. Patent Application Publication No. 2003/0087270 A1 (Schlegel et al.) teaches assessing whether a patient is afflicted with cervical cancer by a process comprising comparing the level of expression of KCNAB1 (i.e., the polypeptide encoded by the marker comprising the disclosed polynucleotide sequence of SEQ ID NO: 104) in a patient sample and the normal level of expression of the protein in a control, wherein a significant increase in the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with cervical cancer; see entire document (e.g., claim 4; paragraphs [0008]; [0047] and [0048]; [0058]; Table 1; and paragraphs [0316] and [0324]). Schlegel et al. teaches, as used therein, "cervical cancer" includes carcinomas (e.g., carcinoma in situ, invasive carcinoma, metastatic carcinoma) and pre-malignant conditions (e.g., dysplasia, including CIN or SIL); see, e.g., paragraph [0008]. Schlegel et al. teaches the process is used to assess whether

the patient is afflicted with cervical adenocarcinoma or squamous cell carcinoma of the cervix; see, e.g., paragraph [0009]. Schlegel et al. teaches an analysis of cervical tumor specific cDNA clones by transcription profiling using mRNA from 12 cervical tumors, 5 CIN III, 5 CIN I and 12 normal cervical tissues indicated that the gene encoding this protein (i.e., the *marker*) is overexpressed in cervical cancer (paragraphs [0316] and [0324]). Schlegel et al. teaches antibodies and fragments thereof that bind specifically with this protein; see, e.g., paragraph [0007]. Schlegel et al. teaches the level of expression of the protein in the samples acquired from the patient and/or control subjects is determined using immunoassays that employ these antibodies or fragments thereof; see, e.g., paragraphs [0047] and [0048]. Schlegel et al. teaches the marker is overexpressed by as factor of at least two, three, four, five or ten, relative to the expression level of the marker in a control sample (e.g., sample from a healthy subjects not having the marker associated disease); see, e.g., paragraph [0067]. Additionally, Schlegel et al. teaches the expression level of the marker in the sample acquired from a patient afflicted with cervical cancer differs significantly from the level of its expression in the control; see, e.g., paragraph [0067]. Schlegel et al. teaches Schlegel et al. teaches the samples comprise cells obtained from the patient or the control subject; see, e.g., paragraph [0046]. Schlegel et al. teaches the cells of which the samples are comprised may be found in a cervical smear, which is collected, for example, by a cervical brush; see, e.g., paragraph [0046]. Schlegel et al. teaches the samples may be fluids collected by vaginal rinsing; see, e.g., paragraph [0046]. Schlegel et al. teaches the disclosed process for assessing whether a patient is afflicted with cervical cancer comprises comparing the expression levels of a plurality (e.g., at least 3, or at least 5) of other markers in the sample acquired from the patient and the corresponding levels of expression in samples acquired from control subjects; see, e.g., paragraph [0051].

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1 and 18-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 4 of copending Application No. 11/510,530. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Copending claim 4 is directed to a method for assessing whether a patient is afflicted with cervical cancer, said method comprising comparing the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1, and the normal level of expression, wherein a significant increase in the level of expression in the patient sample is an indication that the patient is afflicted with cervical cancer.

Table 1 of the copending application discloses a marker comprising the polynucleotide sequence of SEQ ID NO: 104, which is identical to marker M666 of the

instant application, which comprises the polynucleotide sequence of SEQ ID NO: 29 and encodes KCNAB1 (i.e., the polypeptide of SEQ ID NO: 30).

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1 and 18-21 are directed to an invention not patentably distinct from claim 4 of commonly assigned copending Application No. 11/510,530. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the above provisional rejection of claims 1 and 18-21 on the ground of nonstatutory obviousness-type double patenting.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 11/510,530, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

21. No claim is allowed.

22. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. WO 2002/101075 A2 (Schlegel et al.) teaches the overexpression of a marker (i.e., ACF122880; SEQ ID NO: 105), which is identical to marker M666, in cervical cancer, as compared to normal cervical tissue. U.S. Patent Application Publication Nos. 2003/0138792 A1 and 2002/0009724 A1 teach markers of cervical cancer. Chen et al. (*Cancer Res.* 2003 Apr 15; **63**: 1927-1935) and Cheng et al. (*Int. J. Cancer.* 2002; **98**: 419-426) teach the identification of cervical cancer markers.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr

December 4, 2006